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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/683,258	12/05/2001	Kemin Zhou	3418	1011

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EXAMINER	
ZHOU, SHUBO	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/683,258	ZHOU, KEMIN	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and request for reconsideration in the communication filed on 11/21/05 are acknowledged and the amendments entered.

Claims 21 and 23-32 are currently pending and under consideration.

Withdrawn Rejections/Objections

The new matter rejection to the specification and drawings set forth in the previous Office action mailed 5/19/05 is hereby withdrawn in view of applicants' amendment to the specification and drawings, specifically the cancellation of the new sequences of SEQ ID NOS 5 and 6.

The new paper copy, CRF and statement under 37 CFR 1.821(f) filed 11/21/05 have been received and entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pugh et al. (Genome Biology, Vol. 2, pages 1013.1-1013.3, 2001) in view of Walt, D.R. (Science, Vol. 287, pages 451-452, 1/21/2000).

The claims are drawn to a method for obtaining a profile of protein binding to genomic DNA of a biological sample, comprising obtaining a plurality of candidate genomic fragments by DNA foot printing from genomic DNA bound by a plurality of proteins, eliminating unbound genomic DNA, and detecting the candidate fragments by hybridizing with a collection of nucleic acid probes that are immobilized on a collection of beads or optical fibers.

Pugh et al. disclose binding transcription factors, which are proteins, to their DNA on a genomic-wide scale in yeast as a biological sample (page 1013.1 , col. 1, second paragraph), which represents a profile of such binding. Pugh et al. disclose using chromatin immuno-precipitation (ChlP) assay and DNA microarrays for detection of the DNA bound to the proteins (page 1013.1, col. 1, second paragraph). The instant specification defines a "candidate fragment" as "a nucleic acid fragment that contains information about protein nucleic acid interactions" (paragraph 0022). Pugh et al. disclose covalently cross-linking proteins to DNA (a well known form of in vivo foot-printing), purifying the cross-linked DNA via antibodies (elimination of

unbound genomic DNA), fluorescently labeling the enriched DNA fragments (candidate fragments), and detecting them via hybridization to DNA probes on a glass slide of microarray (page 1013.1, col. 1, third paragraph to col. 2, first paragraph). Pugh et al. further disclose various transcription factors binding to genomic regions (page 1013.2, col. 2, second paragraph), which represents DNA bound by a plurality of proteins. Pugh et al. also disclose that 10 regions were bound by Gal4; 29 regions were bound by Ste12; 163 regions were bound by Swi4 and 87 regions were bound by MBF transcription factor (page 1013.2, col. 2, second paragraph) wherein the later two data figures represent at least 50 proteins binding to genomic regions. Pugh et al. disclose the use of intergenic and intragenic (open reading frame) probes (page 1013.1, col. 2, first paragraph), which means the genomic sequences of interest contain genic regions. Pugh et al. disclose that genome-wide location analysis coupled with gene-expression profiling and searches for consensus sites will potentially identify direct effectors of complex gene expression program (page 1013.3, col. 1, third paragraph).

Pugh et al., however, do not explicitly disclose detecting of the candidate fragments by hybridizing to nucleic acid probes that are immobilized on a collection of beads or optical fibers.

Walt teaches a new nucleic acid array referred to as bead-based fiber-optic array for nucleic acid hybridization and detection. Walt discloses that bead arrays are assembled on an optical fiber substrate. See title and page 451, left column. Walt also teaches that fiber-optic oligonucleotide arrays can be prepared by attaching DNA probes to microspheres and then filling each well with a microsphere carrying a different DNA probe. See the paragraph bridging page 451 and 452. Walt also discloses that typical image arrays contain between 5000 and 50,000 individual fibers. See page 451, right column.

Walt states that the advantage of optical fiber sensors are their small size and flexibility, and such features enable the sensors to be placed directly into sample solutions of DNA for immobilizing DNA thereon, rather than bringing the DNA samples to the substrate surface as in the case of glass slide microarray. See page 451, middle column. Thus, sample sizes of about 1 microliter enable DNA to be detected after a limited number of amplification cycles. See page 452, middle column, bottom paragraph. In addition, Walt discloses that another advantage of bead-based optical fiber array is that a simple high temperature denaturation or organic solvent treatment can accomplish dehybridization, and hence fiber-optic microarrays have been used for over 100 hybridization-dehybridization cycles with less than 2% degradation. See page 452, right column.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method by Pugh et al. such that bead-based optical fiber arrays are used in place of glass slide array to take full advantage of the superiorities of optical fiber arrays as disclosed by Walt and detailed above.

As to claims 23-28, which recite a particular number of nucleic acid probes, such as 10,000 in claim 23, or recite a different length for the nucleic acid probe on the array, the difference between what is disclosed by Pugh et al. and Walt and the what is required by the instant claims is the size of the microarray with different numbers and length of the probes thereon. The court in *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) held that "mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled." 531 F.2d at

1053, 189 USPQ at 148. Further, in *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), cert. denied, 469 U.S. 830, 225 USPQ 232 (1984), the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device. Also see MPEP 2144.04. In the instant case, claims 23-28 merely recite step using a microarray that has a different size, and thus with different number of probes, or a different length for the probes immobilized thereon than what is disclosed in the cited references, and is thus not patentably distinct from the methods disclosed by a combination of Pugh et al. and Walt.

Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pugh et al. (Genome Biology, Vol. 2, pages 1013.1-1013.3, 2001) in view of Walt, D.R. (Science, Vol. 287, pages 451-452, 1/21/2000), as applied to claims 21 and 23-28 above, further in view of Shoemaker et al. (Nature, Vol. 409, pages 922-923, 2001).

The claims are drawn to a method for obtaining a profile of protein binding to genomic DNA of a biological sample, comprising obtaining a plurality of candidate genomic fragments by DNA foot printing from genomic DNA bound by a plurality of proteins, eliminating unbound genomic DNA, and detecting the candidate fragments by hybridizing with a collection of nucleic acid probes that are immobilized on a collection of beads or optical fibers. The probes on the arrays are oligonucleotides that tile genomic sequences of interests.

As applied to claims 21 and 23-28 above, the combination of Pugh et al. and Walt teaches such a method. However, Pugh et al. and Walt et al. do not explicitly recite using a microarray have probes thereon that tile a genomic region of interest.

Shoemaker et al. disclose a method of using tiling arrays containing overlapping oligonucleotides that blanket an entire genomic region of interest for assaying gene expression data. Shoemaker et al. state that Such approach of using tiling arrays provides a higher resolution view of gene structure and potentially reveals exons not identified by current gene prediction algorithms and also provide information about alternative splicing.

Since the combination of Pugh et al. and Walt provide a method of finding the genomic locations of the binding site of transcription factors (proteins), and since Pugh et al. disclose that transcription factors would bind to both intergenic and intragenic sites but the intragenic sites are not bound by their cognate factor and are not functional, it would have been obvious to one of ordinary skill in the art that a higher resolution of the gene structure in terms of the exact location of the protein binding would have been desired. Thus, one having ordinary skill in the art would have been motivated by Shoemaker et al. to modify the methods of Pugh et al. and Walt to utilize tiling arrays to blanket the regions of interest for the detection of the genomic regions that bind to the transcription factors to take full advantage of the tiling arrays in order to determine the precise location of the protein binding site in the genome, intergenic or intragenic, and if it is intergenic, whether it is in the promoter of the gene.

As to claim 32, which recite at least one of the binding proteins is unknown, Pugh et al. disclose that "although SBF appears to be bound to many intergenic sites, it is perplexing that deletion of its Swi4 subunit has little effect on the expression of putative SBF target genes," and

Pugh et al. suggest that it is possible that additional or redundant transcription programs direct the expression of these genes." See page 1013.3, left column. Thus, Pugh et al. implicitly disclose or suggesting other unknown proteins involving in the transcription of, and thus binding to, these genes, in addition to SBF.

Applicant's arguments filed 11/21/05 have been fully considered but they are not persuasive. The argument is on the ground that Pugh fails to disclose or suggest using microarray on beads or optical fibers for the hybridization, and the disclosure of small size and flexibility of fiber optic array by Walt will not be motivation to combine the references and will not benefit the invention. This is not found persuasive because, as set forth above, the motivation to combine the references for using microarray on beads or optical fibers for the hybridization comes from Walt. Furthermore, the motivation is not just the advantage of small sample size and flexibility of optic array, but rather all the advantage of fiber optic array as a whole. As set forth in the previous Office action, in addition to the advantage of having small size and flexibility for optical fiber sensors, Walt also discloses that another advantage of bead-based optical fiber array is that a simple high temperature denaturation or organic solvent treatment can accomplish dehybridization, and hence fiber-optic microarrays have been used for over 100 hybridization-dehybridization cycles with less than 2% degradation. See page 452, right column. All these, especially the repeated use of one array for multiple hybridization and dehybridization, would have been attractive features that would motivate one of ordinary skill in the art to modify the method of Pugh to use fiber optic array in lieu of glass slide array.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL.

Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

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